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Is levetiracetam more effective than phenytoin in seizure cessation in children with convulsive status epilepticus that don't respond to first-line treatment?

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Is levetiracetam more effective than phenytoin in seizure cessation in children with convulsive status epilepticus that don't respond to first-line treatment?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not "Is levetiracetam more effective than phenytoin in seizure cessation in children with convulsive status epilepticus that don't respond to first-line treatment?"

Study design: Systematic review of three randomized controlled trials (RCTs) published in peer-reviewed journals in English in 2019.

Data Sources: Three RCTs published in peer reviewed journals were found using Alt HealthWatch, AMED, CINAHL Plus, and Scopus.

Outcome(s) Measured: Clinical cessation of seizure, defined as cessation of continuous rhythmic clonic activity, was measured by the investigator after infusion of treatment.

Results: The study by Dalziel et al. showed a higher rate of seizure cessation in the phenytoin group compared to the levetiracetam group as well as a clinically significant NNT of -10. However, with a p-value of 0.18 and a 95% CI of -23.6 to 4.2 the results were not statistically significant. In the study by Noureen et al. the rates of seizure cessation in the levetiracetam group were significantly higher than those in the phenytoin group (P-value = 0.01). In the study by Lyttle et al. there was a higher rate of seizure cessation in the levetiracetam group compared to the phenytoin group along with an NNT of 10, however the results were not statistically significant with a p value of 0.20.

Conclusions: The only study in this selective EBM review to yield statistically significant results showed that levetiracetam is more effective than phenytoin in seizure cessation in children with convulsive status epilepticus that don't respond to first-line treatment. Due to the variability of the results and limitations of each study, further research is needed to provide a more concrete answer to the question at hand. Additionally, studies analyzing the safety and efficacy of using both phenytoin and levetiracetam together as second line treatment may provide critical information regarding the treatment of CSE in the future.

Key Words: levetiracetam, children, convulsive status epilepticus, randomized controlled trial

INTRODUCTION

Convulsive status epilepticus (CSE) is a neurological emergency that is defined as an unremitting seizure lasting longer than 5 minutes or multiple clinical seizures without interictal return to baseline. CSE can affect anyone, however it is most commonly seen in patients with a history of a seizure disorder who have had a recent change in their mediation regimen or are noncompliant with their medications. Other causes in children include head trauma, infection, fever, hypoxia, and cerebral malformations. If not treated in a timely manner, CSE can lead to various neurologic sequelae, permanent neurodisability, or even death.

In the pediatric population, CSE is the most common neurological emergency worldwide.[1] The annual incidence is 20 per 100,000 children and accounts for 1-2% of all emergency department visits.[2] The estimated cost of CSE in a child is $9,000 per admission, but the annual direct costs of CSE in the USA are estimated around $4 billion dollars.[3] With 34% of children developing neurologic sequelae and 3-5% resulting in mortality, providers need to be quick to recognize and promptly treat CSE. [4] Physician assistants (PAs) have had an increasing presence in emergency departments across the US and the need for them continues to rise. With this change comes an opportunity for PAs to have a more involved role in critical care scenarios such as CSE.

While the exact cause of CSE is unknown, recent research suggests that $GABA_A$ inhibition becomes less effective and glutamates excitatory actions are enhanced.[5] The longer CSE lasts, the harder it is to terminate the seizure, leading to a greater risk of morbidity, including neurologic complications such as neurodisability, learning disabilities, and drug resistant epilepsy. The first line pharmacologic treatment in CSE is a benzodiazepine, most commonly lorazepam or midazolam. If the seizure persists after 2 doses, second line therapy

most commonly is with phenytoin, but other options include levetiracetam, valproate, and phenobarbital. When these measures fail, patients require rapid sequence induction (RSI) and intubation. Research regarding second line treatment options is widely inconsistent. Although phenytoin is effective in around 60% of patients, it has an extensive side effect profile and can cause fatal cardiac arrythmias. Levetiracetam is a broad-spectrum anticonvulsant that has become increasingly popular because it has fewer adverse events and minimal drug interactions. Although phenytoin and levetiracetam are both indicated as second line therapies, this paper evaluates whether levetiracetam is more effective than phenytoin in cessation of CSE in children that don't respond to first line therapy.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Is levetiracetam more effective than phenytoin in seizure cessation in children with convulsive status epilepticus that don't respond to first-line treatment?"

METHODS

All articles were found using Alt HealthWatch, AMED, CINHL Plus, and Scopus. The keywords used were levetiracetam, children, convulsive status epilepticus, and randomized controlled trial. The studies were all published in peer-reviewed journals that were published in English in 2019. Articles were chosen based on the relevance to my clinical question and whether or not results were measured in POEMs. The inclusion criteria for this review were RCTs that were peer reviewed, studies published in English after 2010, and subjects ages birth to 18 years. Exclusion criteria were studies published before 2010, subjects over the age of 18, and studies not published in English.

Three randomized controlled studies were selected for this review. Studies included patients under 18 that presented to the emergency department with CSE that did not respond to first line treatment with benzodiazepines. The interventions included levetiracetam 40 mg/kg IV and phenytoin 20 mg/kg IV. The efficacy of each drug was measured by whether or not seizure cessation occurred, which was determined by the investigator of each clinical trial.

The demographics and characteristics of the studies included in this review are outlined below in table 1. The statistical significance of the outcomes measured were determined by ABI, RBI, NNT, p value, and CI.

OUTCOMES MEASURED

All studied included in this review measured the effectiveness of interventions based off of seizure cessation. This was determined by the investigators of each study who visually evaluated the patients and determined whether there was clinical cessation of seizure activity. In Dalziel et al., the senior most treating physician examined participants for increased tone, jerking movements including nystagmoid eye movements, and level of consciousness based off of the Alert, Voice, Pain, Unresponsive scale five minutes after the end of the drug infusion.[4] Continued seizure activity was defined as increased tone or increased jerking movements. The primary outcome in this study was video recorded when possible to be further reviewed by two emergency physicians and one neurologist to assess for observer bias.[4] In Noureen et al., the outcome was measured 30 minutes after the end of the drug infusion by the senior treating physician who assessed seizure activity based on increased tone, jerking movements, and the level of consciousness.[6] In Lyttle et al., the treating clinician continuously assessed for seizure cessation, as defined by cessation of all rhythmic clonic activity, and measured the time from randomization to cessation of seizure.[1]

Table 1. Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/ D	Interventions
Dalziel, 2019 (1)	RCT	234	3mo -16 yrs	Children aged 3 mo- 16 yrs with CSE that failed first line therapy with 2 doses of a benzodiazepine	Children previously enrolled in the study, regular use of phenytoin or levetiracetam, administration of second-line anticonvulsants in the past 24 h, CI or allergy to phenytoin or levetiracetam CSE due to major head injury	37	Phenytoin 20mg/kg IV or IO infused over 20 minutes diluted 1:4 with 0·9% sodium chloride vs. levetiracetam 40mg/kg IV or IO infused over 5 minutes diluted 1:1 with 0·9% sodium chloride
Noureen, 2019 (2)	RCT	624	1yr-14yr	Male and Females 1–14 years with generalized CSE who did not responding to two doses of diazepam	Received treatment other than benzodiazepine, on assisted ventilation, CSE secondary to hypertensive encephalopathy, head injury, kidney or liver ds, or electrolyte derangement, hypotension symptoms	24	Levetiracetam IV 40 mg/kg infused over 15 minutes vs. phenytoin 20 mg/kg over 30 minutes
Lyttle 2019 (3)	RCT	404	6 mo-18yr	Children of either sex, aged 6 months to under 18 years, presenting with CSE that required second-line treatment	Those who did not require second line treatment Those who did not consent	118	Levetiracetam IV 40 mg/kg infused over 5 minutes vs. phenytoin 20 mg/kg over 20 minutes

RESULTS

In the ConSEPT study by Dalziel et al., 234 children between ages three months and 16 years who presented to 13 qualifying emergency departments in Australia and New Zealand with CSE that failed first line therapy with 2 doses of benzodiazepines were assessed.[4] These individuals were selected based on the inclusion and exclusion criteria noted above in table 1. Participants were randomly assigned using a computer-generated sequence to either receive 20mg/kg of phenytoin or 40mg/kg of levetiracetam intravenously or intraosseous.[4] After randomization, 114 participants were assigned to receive phenytoin and 119 participants were assigned to receive levetiracetam. Of the 115 participants randomly assigned to receive phenytoin, one participant refused consent, three were intubated before phenytoin was administered, and 15 had cessation of seizure activity before administration of the drug.[4] Of the 119 participants randomly assigned to receive levetiracetam, two had to be intubated prior to receiving the drug and 16 had seizure cessation before starting levetiracetam.[4] The remaining 96 participants who received phenytoin and remaining 101 participants that received levetiracetam were included in the modified intention-to-treat population analyzed in this review.

Participants were evaluated by the most senior treating physician five minutes after the drug infusion was completed. In the levetiracetam group, 46 participants or 46% achieved clinical cessation of seizure (Table 2).[4] In the phenytoin group, 53 participants or 55% achieved clinical cessation of seizure (Table 2).[4] When comparing the two treatment groups, there was not a statistically significant difference ($p= 0.18$).[4] Additionally, the 95% confidence interval of -23.6 to 4.2 is wide and crosses 0, suggesting the treatment effect is not precise (Table 2).[4] The NNT was -10, which is a large negative treatment effect suggesting that if 10 people are treated

with levetiracetam, one fewer participant would have seizure cessation than if they received phenytoin. The RBI was -0.18 and the ABI was -0.10 (Table 3).

Noureen et al. assessed 624 children ages one to 14 years old who presented to the emergency department of The Children's Hospital and The Institute of Child Health in Multan, Pakistan between January 2014 to June 2018 with CSE that did not respond to two doses of diazepam.[6] Refer to Table 1 for specific inclusion and exclusion criteria. All participants were randomly assigned using a sealed envelope system to either receive levetiracetam 40 mg/kg IV infused over 15 minutes or 20 mg/kg phenytoin IV infused over 30 minutes.[6] After randomization 300 participants were allocated to the levetiracetam group and 324 participants were allocated to the phenytoin group. However, 24 participants randomized to the phenytoin group either did not consent or withdrew from the study, leaving 300 participants to receive phenytoin.[6] Participants were evaluated from the start of the infusion until 30 minutes after completing the infusion. In the levetiracetam group 278 participants or 92.7% achieved seizure cessation (Table 2).[6] In the phenytoin group 250 participants or 83.3% achieved seizure cessation (Table 2).[6] The p-value was 0.01, indicating a statistically significant difference between the treatment groups (Table 2).[7] No confidence interval was provided. The NNT was 17, suggesting a large positive treatment effect. The RBI was 0.09 and the ABI was 0.06 (Table 3).

In the EcLiPSE study by Lyttle et al., 404 children aged six months to 18 years that presented at 30 different UK emergency departments between July 2015 and April 2018 with CSE requiring second line treatment were assessed.[1] Specific inclusion and exclusion criteria can be found in Table 1. A statistician with no further involvement in the study produced a computer-generated randomization schedule and delivered them to eligible sites in tamper-proof envelopes for treating clinicians to open after confirmation of eligibility.[1] Of the 404

participants, 212 were assigned levetiracetam and 192 were assigned phenytoin. In the levetiracetam group, 51 participants did not require second line treatment and nine participants did not consent, leaving 152 participants for analysis.[1] In the phenytoin group, 42 participants did not require second line therapy and 16 declined consent, leaving 134 participants for analysis.[1]

The primary outcome measured in the EcLiPSE study was the time from randomization to cessation of seizure. In order to maintain consistency with the other studies, whether or not each trial drug provided seizure cessation was analyzed to determine drug efficacy rather than analyzing the length of time to seizure cessation. Seizure activity was terminated in 106 participants or 70% in the levetiracetam group and 86 participants or 64% in the phenytoin group (Table 2).[1] There was not a statistically significant difference between the two treatment groups (p=0.20).[1] No confidence interval was provided for this outcome. Despite an insignificant p-value, the NNT was 10, suggesting a large positive treatment effect (Table 3). The RBI was calculated as 0.11 and the ABI as 0.10 (Table 3).

Table 2. Seizure Cessation, p-value, and 95% CI by Study

Study	Levetiracetam	Phenytoin	p-value	95% CI
Dalziel et al.	46 (46%)	53 (55%)	0.18	-23.6 to 4.2
Noureen et al.	278 (92.7%)	250 (83.3%)	0.01	--
Lyttle et al.	106 (70%)	86 (64%)	0.20	--

Table 3. Calculations for Treatment by Study

Study	RBI	ABI	NNT
Dalziel et al.	-0.18	-0.10	-10
Noureen et al.	0.09	0.06	17
Lyttle et al.	0.11	0.10	10

DISCUSSION

Convulsive status epilepticus is one of the most commonly encountered neurological emergencies in emergency departments around the world. The treatment is complex and

constantly evolving. Beyond first line treatment with benzodiazepines, there is a lack of strong evidence to guide additional pharmacologic treatment prior to RSI and intubation. While the aim of this selective review was to determine if levetiracetam is more effective than phenytoin in seizure cessation in children with convulsive status epilepticus that don't respond to first-line treatment, the articles in this review did not provide a clear answer.

All three studies evaluated seizure cessation. Dalziel et al. demonstrated higher rates of seizure cessation in the phenytoin group than in the levetiracetam group, but the results were not statistically significant.[4] An additional feature of the Dalziel et al. study was that some participants who did not respond to second line treatment were given the alternate study drug immediately following failure of the first.[4] They found that this additional treatment reduced the need for RSI and intubation by about 50%, but formal studies are needed for further investigation.[4] Lyttle et al. and Noureen et al. demonstrated higher rates of seizure cessation in the levetiracetam group than the phenytoin group, however only Noureen et al. showed a statistically significant difference between the two treatment groups.[1,6] While the Lyttle et al. study did not show a statistically significant difference between treatments, the NNT was 10, suggesting a large treatment effect and clinical significance.[1] Of consideration, the seizure cessation rates of both levetiracetam and phenytoin were significantly higher in the Noureen et al. study than the other studies analyzed in this selective review, potentially due to specific characteristics of study participants.[6] Further studies are needed to solidify the findings.

There were various limitations to all studies analyzed in this selective review. First, the outcomes were all subjective based on the treating clinician and their clinical judgment. Although this could have played a role in the study outcomes, it mirrors real-life clinical practice in the sense that EEGs are not typically available in the setting of CSE and outcomes are

continuously assessed by the treating physician.[4] Additionally, the physicians were not masked to treatment allowing for possible bias. However, given the life-threatening nature of CSE, there is a low probability that this occurred. Next, there was a longer time to assessment of seizure cessation in the phenytoin group due to the slower infusion rate.[1,4,6] This could have allowed more time for the first line therapies to take effect or a natural decline of seizure activity. Another factor to consider when interpreting the findings is the extensive use of levetiracetam as a maintenance therapy.[5] Phenytoin is not widely used as maintenance therapy due to its adverse effects. For example, in Lyttle et al., 55 participants were taking levetiracetam as a maintenance therapy compared to 1 participant taking phenytoin as maintenance therapy.[1]

There are additional limitations to consider when analyzing the studies by Dalziel et al. and Lyttle et al. When videos of the primary outcomes in Dalziel et al. were further reviewed by two emergency physicians and one neurologist to assess for observer bias, the group unanimously disputed the outcomes of four participants in the phenytoin group and three participants in the levetiracetam group.[4] Although the independent reviewers found evidence conflicting with the initial assessment, it occurred in similar numbers in each of the treatment groups.[4] Finally, a limitation of the Lyttle et al. study was that three participants in the levetiracetam group received phenytoin but were still analyzed in the levetiracetam group.[1] However, due to the fact that the three participants only made up 2% of the levetiracetam group, it is unlikely this error significantly altered the results.

CONCLUSION

Although the use of levetiracetam as a second line treatment for children with CSE seemed promising, the three studies in this selective EBM review did not agree on whether or not it is more effective than phenytoin in cessation of seizures. Similar to this review, previous

studies regarding the use of phenytoin and levetiracetam as second line treatment in patients with CSE have provided contradicting or inconclusive results. The variability in the results of the three studies selected for this EBM review suggest future studies are necessary to provide a more concrete answer. Currently there is more research being conducted on adults with CSE rather than children with CSE, making continued research on second line treatments in pediatric CSE even more important.[1]

While the results of this systematic review do not show that one drug is more efficacious than the other in seizure cessation, it does suggest that both levetiracetam and phenytoin are effective in cessation of CSE in children who do not respond to first line treatment. An analysis regarding safety and tolerability of phenytoin and levetiracetam may help provide more insight into which drug would be a better second line option. As previously stated, the Dalziel et al. study found that the use of phenytoin and levetiracetam back-to-back as second line treatment improved seizure cessation rates and decreased the need for RSI by 50%.[4] Additional studies analyzing the safety and efficacy of using both phenytoin and levetiracetam together as second line treatment are needed and may provide critical information regarding the treatment of CSE in the future.

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